IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

MacLEAN et al Atty. Ref.: **620-73**

Serial No. **08/776,350** Group: **1642**

Filed: **April 18, 1997** Examiner: **Ungar**

For: **TREATMENT OF CANCER USING HSV MUTANT**

* * * * * * * * * * * *

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

RULE 132 DECLARATION

I, Garth Cruickshank, Ph.D., FRCS, hereby declare:

1) I am a Professor of Neurosurgery at University Hospital Birmingham, Edgbaston, Birmingham, B15 2TH;

2) My special interests special interests are tumours and vascular abnormalities of the brain. A copy of my professional resume is attached.

3) I have reviewed the above-identified application, including the claims, and the cited art, as further discussed below.

4) I have read and understood U.S. patent no. 5,585,096 and the Office Actions dated 22 September 2000 and 5 April 2001 and offer the following comments relating to the reference in U.S. patent no. 5,585,096 to the treatment of melanoma cells.

5) I believe that a person of ordinary skill in the art working in the neuro science field in 1994 would not have concluded from the details provided in U.S. patent no. 5,585,096 that extracranial human melanoma were treatable by use of HSV which contains a deficiency in the y34.5 and ribonucleotide reductase genes.

6) It is not disputed that the production of an avirulent strain of HSV having a modification such as a deletion in the y34.5 gene was possible in 1994. However, the application of an avirulent HSV strain to the treatment of neoplastic cells was not considered realistic.

7) It has been known for a considerable time that HSV inhabits cells of the nervous system. Thus, it may have been considered reasonable that avirulent strains of HSV could have been used to inhabit diseased nervous system cells following the replication of the virus.

8) U.S. patent no. 5,585,096 provides experimental evidence supporting the view

that avirulent HSV strains can be used to treat abnormal neuronal cells. In fact the patent illustrates the use of a replication competent HSV vector with defective expression of the γ34.5 and the ribonucleotide reductase gene in the treatment of primary brain tumours. The patent exemplifies the use of an avirulent strain of HSV on human brain tumours and human glioma.

9) The results provided in U.S. patent no. 5,585,096 show that the avirulent strain of HSV may have been effective at killing tumours of a neuronal origin. There is no data however provided in the patent and no supporting evidence referred to to support the contention that the avirulent HSV strain could have been used in the same way to kill tumour cells of a non-neuronal origin.

10) I note that the patent makes reference to intracranial melanoma. However it seems to me that one of ordinary skill in the art would have appreciated that the inclusion of intracranial melanoma in the list of tumour cells provided in column 3 lines 49 to 58, for example, of the patent is more of a catch-all list of what might be hoped-for rather than a reasoned claim that usefully had envisaged a specific, credible extracranial application, particularly as the main thrust of the patent is aimed at brain tumours, and no examples of other sorts of tumours are given. On the basis of this alone, I do not believe that people of ordinary skill in the art working in this field in 1994 would have accepted or expected that evidence of treatment of neuronal tumours could

have pre-supposed the same level of success in the treatment of non-neuronal tumours.

11) It was well known in 1994 that wild type virus had cell type and cell cycle specific activity which would imply that failure of replicative cytotoxicity might well occur in some cells. The fact that only a limited type of cell selection even for neuronal tumours was described in U.S. patent no. 5,585,096 implies that the cytotoxic process ascribed to the double mutant vector, failed in some cell types. This again supports the view that such avirulent HSV mutants could not have been reasonably expected to work in the suggested list of cell types on the basis of existing practical methodology at the time.

12) It is not evident to me that a convincing argument has been made by U.S. patent no. 5,585,096 for extending the principle of replicative cytotoxicity to such a wide variety of non-neuro cell types based on the presented cell response quoted in the patent. Even the extracranial, subcutaneous xenografis were performed using human glioma cell line U-87MG, and no other cell lines.

13) I do not believe any evidence has been provided in U.S. patent no. 5,585,096 that would have persuaded an ordinarily skilled worker in this field in 1994 that such virulent strains of HSV could be successfully used to treat tumours of a non-

neuronal origin, particularly given that it was known that HSV was cell specific and cell cycle specific and was known to selectively inhabit neuronal cells.

14) I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

By _____
Garth Cruickshank, Ph.D., FRCS

Date: 24/02/02

CURRICULUM VITAE

OF

GARTH STUART CRUICKSHANK
BSc, PhD, MBBS, FRCS(Ed), FRCS(Eng), FRCS(SN)

PROFESSOR OF NEUROSURGERY
ACADEMIC DEPARTMENT OF NEUROSURGERY
CLINICAL NEUROSCIENCE
QUEEN ELIZABETH HOSPITAL
and
UNIVERSITY OF BIRMINGHAM
EDGBASTON
BIRMINGHAM

PERSONAL

Born: 24 January 1951

Present appointment:

1997 - Professor of Neurosurgery Academic Department of Neurosurgery University of Birmingham
Honorary Consultant Neurosurgeon University Hospital Birmingham NHS Trust

Previous appointment:

1994 - 1997 Senior Lecturer and Honorary Consultant Neurosurgeon Institute of Neurological Sciences Glasgow

NHS ACTIVITY

In Glasgow (Senior Lecturer) 1994 - 1997
Introduction of IT policy, leading to integration of neurosciences with PAS and all Lab services.
Introduction of Neurosciences IT clinical database system for complete activity analysis.
Chairman of R&D Committee.

In West Midlands 1997 -
Cancer Site Leader Neuro-oncology - involves weekly additional meetings to consider audit programmes and supervision of service, research and quality control.
Audit Committee.
Development of Head Injury Management Strategy for the Trust.
Development of Stereotactic Radiosurgery and Steering Committee - I am responsible for this programme and run fortnightly planning meetings and monthly project meetings. I shall introduce Conformal treatment this year.
BHA (Head Injury policy and conference April 1998).
Development of new care pathways and networks for support of 'new' hospital proposal.
Formation of Trauma Group between Selly Oak Hospital and Queen Elizabeth Hospital.

NHS REGIONAL ACTIVITY

HST committee in Neurosurgery and frequent member of AACs for SHO, Registrar and now SpR appointments in the West Midlands and UK.
Regional Neuro-oncology Database College trainer in Neurosurgery for Audit.
Member of Cancer Appraisal Assessment Team (3 occasions).
Head Injury - introduction of guidelines to District General Hospital (6 occasions).
Scottish Audit Trauma Group (STAG) member 1995-1997. Examining the provision and analysis of acute services. This formed the basis of the Scottish Acute Services review.

AT NATIONAL AND INTERNATIONAL LEVEL

MRC Brain Tumour Working Group (3 times per year and completion and submission of policy documents and protocols).
Cochrane Collaboration - Neuro-oncology 1998.
Chairman of Data Review Board for Gene Therapy (Novartis) (HSVtk trial) - 2 visits and 7 meetings per annum plus analysis of multicentre trial data in gene therapy (HSVtk) 1996-1999.
Co-editor of British Journal of Neurosurgery 1998 -
Advisor to United Kingdom Brain Tumour Association 1998 -
At the national level I have been involved in various courses to do with the Specialist Neurosurgical exam and have taught on the Glaxo Wellcome Neurosciences Course at Queen Square and at the Royal Society of Medicine Neurosciences Course.
I have given various lectures of an educational nature to the British Association of Neurological Nurses, National Association of Theatre Nurses, Kings College lecture course, and abroad at the Humboldt University of Berlin, the Chinese University in Hong Kong and the Boston Medical Imaging Centre at Harvard University.
I was an invited speaker at the 1998 National Association of Fund Holding Practitioners in Harrogate.
I have also been involved in patient awareness teaching, carer teaching for Headway and the United Kingdom Brain Tumour Association.
Invited speaker 4th Congress European Federation of Neurological Sciences 1999.
Member of the Royal College of Physicians Working Party 1997 on 'the Care of Patients with Malignant Glioma'. This has established the criteria for the provision of a quality service to these patients.
UK Cancer Co-ordinating Committee (UKCCC).
Royal College of Surgeons Appointments Assessor.
DVL Honorary Medical Advisory Panel on Driving and Disorders of the Nervous System.

UNIVERSITY ADMINISTRATIVE WORK

Neurosciences Management Committee.
Neurosciences Consortium.
Boron Neutron Capture administration and Steering Committee.
Higher Degree external examiner Glasgow 1998; Bristol 1998; Birmingham 1998; London 1997, 1998.
External advisor for Senior Academic appointments in the University of Glasgow 1998, Nottingham 1998, Manchester 1998, London 1997, 1998.

RESEARCH ACTIVITIES

Co-holder of MRC grant with Professor Brown and Dr Rampling in Glasgow 1997-1999. This involves a novel trial of mutant HSV1 in the direct treatment of intracranial tumours. Has involved considerable negotiation with GTAC and MCA. The first gene therapy trial of its type in the world and the first using gene therapy in Brain Tumours in the UK.
Co-applicant/holder of MRC collaborative Group with Professor David Kerr. Development of Gene Therapy approaches to Brain Tumours.
Co-holder of EEC (F4) Measurement Initiative with Biospace International and Ecole Superiore Paris. Involves the development of new high resolution Multiwire Gamma Camera systems to enable real-time image directed surgery.
Co-holder of British Brain and Spine Foundation award for David Cooper Aneurysm Study Scotland.

Co-holder of CPSRC aware with Professor Derek Beynon and Dr Nick James to investigate gamma holography (May 1999 onwards).
Local Research Director of MRC ISAT GDC coiling trial.
Local Research Director of STICH intracranial haematoma trial.
Main research interests: Neuro-oncology, Gene Therapy, Image Directed Surgery and Boron Neutron Capture. Review approximately 4 papers per month.

TEACHING ACTIVITIES

In Scotland as Senior Lecturer 1994-1997 I was actively involved in the introduction of the New Undergraduate Medical Curriculum in Glasgow geared solely on a problem based approach to learning.
President of the Chirurgia Medica (GU) 1996-1997.
West Midlands Higher Neurosurgical Training Committee 1997 -. Lecturer on Regional, National and International Courses for trainees in Neurosurgery.
Joint and sole supervisor for Research Degrees.
In addition to year 1, 2 and 4 teaching (lectures and bedside) I have been involved in year 4 project development, year 5 tutorials and teaching.
Organised and placed a number of visiting students and post-graduates over the last year and been responsible for the content of their experience.

IMPORTANT PUBLICATIONS IN THE LAST FIVE YEARS

1. Rampling RP, Cruickshank GS, Lewis A, Hemingway A, Workman P. Direct measurement of PO2 distribution and bioreductive enzymes in human malignant brain tumours. *Int.J.Radiat.Oncol.Biol.Phys* 1994;**29**:427-431
First accepted confirmation of hypoxic nature of glial tumours and its significance for tumour therapeutic resistance.

2. McKie EA, Maclean AR, Cruickshank GS, Lewis AD, et al. Selective in vitro replication of herpes simplex virus type 1 (HSV-1) ICP34.5 null mutants in primary human CNS tumours - evaluation of a potentially effective clinical therapy. *Br J Cancer* 1996;**74**:745-752.
First evidence that mutant replication competent Herpes virus could kill Human Brain Tumours.

3. Rampling R, Cruickshank G, Maclean A & Brown M. Therapeutic replication-competent herpes virus. *Nature Medicine* 1998;**4**:133.
First ever publication of clinical use of replication competent mutant HSV in the clinical situation.

4. Brada R, Cruickshank G. Radiosurgery for brain tumours - Triumph of marketing over evidence based medicine. *British Medical Journal* 1999;**318**: 411.

RECENT PUBLICATION

A Phase 1 study of intratumoural injection with RL1 null mutant herpes simplex virus HSV 1716 type 1 into recurrent malignant glioma. Rampling R, Cruickshank G, Papanastassiou V, Nicol J, Hadley D, Petty R, Harland J, McKie E, Mabbs R, McLean A, Brown M. *Nature Medicine 1999.*

PERSONAL STATEMENT

Since taking up my appointment as Professor of Neurosurgery in July of 1997, I have been heavily involved with the management alterations that have led to the substantial improvement in the regional neurosurgical service in the last 18 months. In particular, we have taken the number of operations from 1,300 to nearly 2,000. This has come about from my participation in the reorganisation of team structures and more efficient use of staff. The use of theatres has been streamlined and brought up-to-date and we have introduced new technologies such as image guided surgery to enhance this process. I am currently introducing real-time image guided technology for the first time in the UK. I have been heavily involved in the acceleration of the stereotactic radiosurgery process and instrumental in bringing in a highly beneficial contract to allow the early introduction of stereotactic radiosurgery service for the West Midlands. I have also been instrumental in helping the Birmingham Health Authority and the Trust to develop a strategy to copy with the complex problem of the referral of head injuries to our regional neurosurgical unit.

My major research interest is in neuro-oncology, particularly in the development of the oncology service. I have analysed the demographics of referral and survival for patients with brain tumours throughout the whole of the West Midlands and developed an efficient database system for capturing this information and providing up-to-date survival figures. I have improved the provision of patient service for neuro-oncology and developed specific out-patient clinics, patient support groups and multi-disciplinary working to ensure appropriate cancer appraisal status. I have introduced new technology for the management of brain tumours including stereotactic radiosurgery, as well as providing important clinical input into the Boron Neutron Capture Programme. Using the above features I have been able to introduce a research-based strategy to the development of new treatments including a programme to introduce Gene Therapy as one of the Phase 2 programmes into the Trust. I am the first neurosurgeon to inject replication competent mutant HSV 1716 (oncotoxic virus) into human brain tumours.

At the national level I have been heavily involved in the development and audit strategies concerned with Gene Therapy, and I am the only neurosurgeon in the United Kingdom recognised by the Gene Therapy Advisory Committee for the use of Gene Therapy in the brain. In this capacity I have been advisor to the Medical Research Council and the Chairman of the Data Review Board for the international trial looking at retroviral HSVtk use in the largest Gene Therapy trial in the world. In addition to these factors I have spoken on neurosurgical matters on several occasions for television and radio and am currently involved in a series of programmes looking at cancer treatments and new technology. In the last few months I have been appointed to the UKCCC and have provided detailed documentation to NICE on stereotactic radiosurgery.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

MacLEAN et al

Atty. Ref.: 620-73

Serial No. 08/776,350

Group: 1642

Filed: April 18, 1997

Examiner: Ungar

For: TREATMENT OF CANCER USING HSV MUTANT

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

DECLARATION OF DEPOSITED MATERIALS

As an authorized representative, and on the instructions of, The University Court of the University of Glasgow, . University Avenue. Glasgow, G12 8QQ, United Kingdom, the assignee of U.S. Patent No. 6,040,169, an assignee of the above-identified application, and the owner of strain HSV 1716, which was deposited with the ECACC PHLC Center for Applied Microbiology and Research, Porton Down, Salisbury, Wilts. SP4 PJG United Kingdom on January 28, 1992, which was assigned the Accession No. V92012803, I declare and state as follows:

- The University Court of the University of Glasgow is the owner of the following deposited biologloal material identified and referred to in the specification of this application and on the attached deposit receipt, international form, under the terms of the Budapest Treaty (hereinafter "the deposit").

Accession No.	Depositor's Reference	Date Deposited
V92012803	HSV 1716	January 28, 1992

- The deposited biological material identified above was made by the MRC Virology Unit, Institute of Virology, Church Street, Glasgow G11 5JR, and assigned to The University Court of the University of Glasgow (hereinafter "the depositor") on 29 June 1998 As the deposit has been deposited and accepted under the terms of the Budapest Treaty on th International Recognition

of the Deposit of Microorganisms for the Purpos s of Patent Procedure, the filing of a viability statement is believed to be unnecessary [37 C.F.R. 1.807(b)]. A copy of the original Viability Statement issued to the MRC pursuant to Rule 10.2 by the International Deposit Authority is also attached however.

- The deposit will be maintained for a period of 30 years from the date of deposit or for the enforceable life of any patent issuing from this application or for a period of 5 years after the date of the most recent request for the furnishing of a sample of the deposited material, whichever is longest.
- The deposit will be replaced should it become contaminated or no longer viable.
- Subject to 37 C.F.R. § 1.808(b), all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent issuing from the above-identified patent application.
- Access to the deposited material is permitted during the pendency of the above-identified patent application to one determined by the Commissioner of Patents and Trademarks to be so entitled under 37 C.F.R. § 1.14 and 35 U.S.C. § 122.

I further declare that all statements made herein of my own knowledge are true and that all statement made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 101 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

By (signature) Kevin Cullen
(Print Name) Kevin Cullen
(Print Title) Deputy Director , Business Development

Date: 26/2/02

BUDAPEST TREATY ON THE INTERNATIONAL
RECOGNITION OF THE DEPOSIT OF MICROORGANISMS
FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

MRC Virology Unit
Institute of Virology
Church Street
Glasgow G11 5JR

VIABILITY STATEMENT
issued pursuant to Rule 10.2 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified on the following page

AME AND ADDRESS OF THE PARTY
WHOM THE VIABILITY STATEMENT
IS ISSUED

DEPOSITOR	II. IDENTIFICATION OF THE MICROORGANISM
e: MRC Virology Unit ress: Institute of Virology Church Street Glasgow G11 5JR	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: V92012803 Date of the deposit or of the transfer: 28.01.92

. VIABILITY STATEMENT

viability of the microorganism identified under II above was tested
28.01.92 [2]. On that date, the said microorganism was

[3] viable

[3] no longer viable

ndicate the date of the original deposit or, where a new deposit or a transfer has been
ade, the most recent relevant date (date of the new deposit or date of the transfer).

n the cases referred to in Rule 10.2(a)(ii) and (iii), refer to the most recent viability
est.

ark with a cross the applicable box.

FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

To
MRC Virology Unit
Institute of Virology
Church Street
Glasgow G11 5JR

NAME AND ADDRESS OF DEPOSITOR

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT
issued pursuant to Rule 7.1 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. IDENTIFICATION OF THE MICROORGANISM

Identification reference given by the DEPOSITOR: HSV1 171.6

Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: V92012803

II. SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION

The microorganism identified under I above was accompanied by:

[X] a scientific description

[ ] a proposed taxonomic designation

(Mark with a cross where applicable)

III. RECEIPT AND ACCEPTANCE

This International Depositary Authority accepts the microorganism identified under I above, which was received by it on 28.01.92 (date of the original deposit)[1]

IV. RECEIPT OF REQUEST FOR CONVERSION

The microorganism identified under I above was received by this International Depositary Authority on (date of the original deposit) and a request to convert the original deposit to a deposit under the Budapest Treaty was received by it on (date of receipt of request for conversion)

V. INTERNATIONAL DEPOSITARY AUTHORITY

Name: Dr Alan Doyle, Curator, ECACC
PHLS Centre for Applied Microbiology & Research, Porton Down,
Address: Salisbury, Wilts. SP4 0JG UK

Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s):

Date: 17 March 1992

1 Where Rule 6.4(d) applies, such date is the date on which the status of international depositary authority was acquired.

Form BP/4 (sole page)

V. CONDITIONS UNDER WHICH THE VIABILITY TEST HAS BEEN PERFORMED[4]

INTERNATIONAL DEPOSITARY AUTHORITY

me:

. Alan Doyle, Curator, ECACC

ress:

S Centre for Applied Microbiology & Research
ton Down, Salisbury, Wilts. SP4 0JG, U.K.

Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s):

Date:

17 March 1992

Fill in if the information has been requested and if the results of the test were negative.

PHLS Public Health Laboratory Service

Centre for Applied Microbiology and Research

This document certifies that Virus Strain
(Deposit ref V92012803) has been accepted
as a patent deposit, in accordance with
The Budapest Treaty of 1977,
with the European Collection of Animal Cell Cultures on
28 January 1992

Dr. Alan Doyle,
Curator.